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Application No.: 10/729,856
Filing Date: December 4, 2003
First Inventor: Manne Satyanarayana REDDY
Art Unit: 1626

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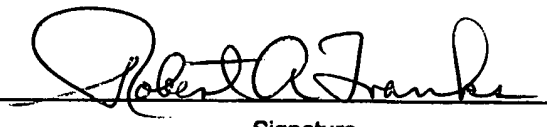

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Robert A. Franks

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28,605
Registration Number, if applicable

908-203-6504
Telephone Number

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Transmittal letter
Certified copy of India Application No. 908/MAS/2002 (28 pages)
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Docket No. BULK 3.0-034

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Manne Satyanarayana REDDY et al. Art Unit: 1626

Application No. 10/729,856 Examiner: E. O. Sackey

Filed: December 4, 2003

For: POLYMORPHIC FORMS OF DIHYDROCHLORIDE SALTS OF CETIRIZINE AND PROCESSES FOR PREPARATION THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

TRANSMITTAL LETTER

To complete the foreign priority claim requirements under 35 U.S.C. § 119 for the subject application, enclosed is a certified copy of the priority application that was filed in India as Application No. 908/MAS/2002, on December 4, 2002.

Please enter the document in the record for this application.

Respectfully submitted,

Robert A. Franks
Reg. No. 28,605
Attorney for Applicants

August 31, 2006

Dr. Reddy's Laboratories, Inc.
200 Somerset Corporate Blvd., Seventh Floor
Bridgewater, New Jersey 08807-2862
Telephone 908-203-6504
Facsimile 908-203-6515

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INDIA

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GOVERNMENT OF INDIA
PATENT OFFICE
Ministry of Commerce and Industry
Department of Industrial Policy and Promotion

It is hereby certified that annexed here to is a true copy of **Complete Specification, Abstract & Drawings** of the patent application as filed and detailed below:-

Date of application : **04-12-2002**

Application No : **908/MAS/2002**

Applicants : **Dr. Reddy's Laboratories Limited, an Indian Company having its registered office at 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh, India**

In witness there of
I have here unto set my hand

Dated this the 23rd day of August 2006
1st day of Bhadrapada, 1928(Saka)

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FORM-2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION
(SECTION 10)

Novel Polymorphic forms of

Dextro and Levo rotatory dihydrochloride salts of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid

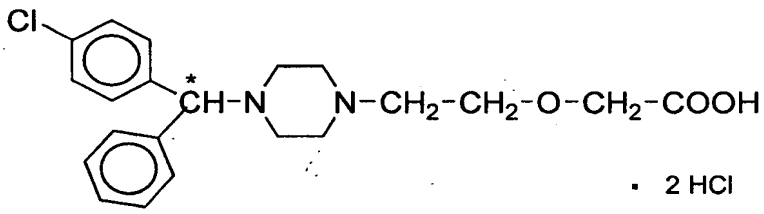
(Dextro and Levo rotatory dihydrochloride salts of Cetirizine)

Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet,
Hyderabad – 500 016, A.P., India

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to novel Polymorphic forms of Dextro and Levorotatory dihydrochloride salts of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Dextro and Levo rotatory dihydrochloride salts of Cetirizine). Herein after Levorotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid is referred as Levorotatory dihydrochloride salt of Cetirizine and Dextrorotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid is referred as Dextrorotatory dihydrochloride salt of Cetirizine for convenience. More specifically, the present invention relates to novel crystalline and novel amorphous forms of Dextro and Levorotatory dihydrochloride salts of Cetirizine. The present invention also relates to process for the preparation of these novel Polymorphic forms of Dextro and Levo rotatory dihydrochloride salts of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Dextro and Levo rotatory dihydrochloride salts of Cetirizine), which can be depicted as following Formula (I).



Formula (I)

Dextrorotatory dihydrochloride salt of Cetirizine is used for the treatment of allergic syndromes such as chronic and acute allergic rhinitis, allergic conjunctivitis, pruritus, urticaria etc. The product was proved to be remarkably free from side effects on the central nervous system.

BACKGROUND OF THE INVENTION

GB 2 225 321 A disclosed the process for the preparation of Dextro and Levo rotatory dihydrochloride salts of Cetirizine, which comprises treating the Levo or Dextro rotatory Cetirizine with hydrochloric acid in acetone.

The journal of Tetrahedron Lett. 37(28), 4837-4840 1996 disclosed the enantio selective synthesis of Dextro and Levo rotatory dihydrochloride salts of Cetirizine and purification via ion exchange chromatography.

Many of the related patents were disclosed the process for the preparation of enantiomers Cetirizine and its salts including dihydrochloride in various methods, but none of these patents were described the existence of crystalline or amorphous forms of dextro or levorotatory dihydrochloride salts of Cetirizine.

During our laboratory experimentation as a part of process development, novel crystalline and amorphous forms of Dextro and Levorotatory dihydrochloride salts of Cetirizine were resulted while crystallizing the pharmaceutically acceptable salts of Cetirizine in different solvents.

Hence, the main aspect of the present invention is to provide novel crystalline and amorphous forms of Dextro and Levorotatory dihydrochloride salts of Cetirizine.

The present invention of novel crystalline form of Dextro and Levo rotatory dihydrochloride salts of Cetirizine is collectively designated as crystalline Form-I for convenience and herein after it is referred as novel crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of Cetirizine.

The second aspect of the present invention is to provide the process for the preparation of novel crystalline form of Dextro and Levorotatory dihydrochloride salts of Cetirizine.

Another aspect of the present invention is to provide the process for the preparation of novel amorphous form of Dextro and Levorotatory dihydrochloride salts of Cetirizine.

The novel crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of Cetirizine is characterized by X-ray powder diffractogram, which has the well-resolved peaks. The pattern of X-ray diffractogram for both dextro and levorotatory dihydrochloride salts of Cetirizine is similar.

The novel amorphous form of Dextro and Levorotatory dihydrochloride salts of Cetirizine is characterized by X-ray powder diffractogram, which has no well-resolved peaks.

Both novel crystalline and amorphous forms of Dextro and Levorotatory dihydrochloride salts of Cetirizine are free flowing and non-solvated solids. These solids are well suitable for pharmaceutical applications.

The processes of the present invention are simple, eco-friendly and easily scalable.

SUMMARY OF INVENTION

The first aspect of the present invention relates to the novel crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of Cetirizine and the process for the preparation there of.

The process for the preparation of crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of Cetirizine comprises the purification of crude dihydrochloride salt of Dextro or Levo rotatory Cetirizine in aqueous keto solvents such as aqueous acetone to afford the novel crystalline Form-I of Dextro or Levo rotatory dihydrochloride salt of Cetirizine.

The second aspect of the present invention relates to the novel amorphous form of Dextro and Levo rotatory dihydrochloride salts of Cetirizine and the process for the preparation there of.

The process for the preparation of novel amorphous form of Dextro and Levo rotatory dihydrochloride salts of Cetirizine comprises the dissolution of crude dihydrochloride salt of Dextro or Levo rotatory Cetirizine in aqueous keto solvents such as aqueous acetone and subjecting the resultant solution to flash distillation under reduced pressure to afford the novel amorphous form of Dextro or Levo rotatory dihydrochloride salts of Cetirizine.

The crystalline or amorphous nature of present invention is characterized by X-ray diffractogram, Differential Scanning Calorimetry thermogram and Infra red spectrum.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

Fig-1 is a diagram showing the X-ray powder diffraction of crystalline Form-I of Dextro rotatory dihydrochloride salt of Cetirizine.

Fig-2 is a diagram showing the X-ray powder diffraction of crystalline Form-I of Levo rotatory dihydrochloride salt of Cetirizine.

Fig-3 is a diagram showing the X-ray powder diffraction of amorphous form of Dextrorotatory dihydrochloride salt of Cetirizine.

Fig-4 is a diagram showing the X-ray powder diffraction of amorphous form of Levorotatory dihydrochloride salt of Cetirizine.

DETAILED DESCRIPTION OF THE INVENTION

The first aspect of the present invention relates to the novel crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of Cetirizine and the process for the preparation there of.

The present invention of novel crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of Cetirizine is characterized by X-ray powder diffractogram. The X-ray powder diffraction pattern of novel crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of Cetirizine of the present invention is measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The novel crystalline Form-I of dihydrochloride salts of Dextro and Levo rotatory Cetirizine of the present invention is having the similar X-ray powder diffractogram pattern there by for our convenience, it is being represented as crystalline Form-I of dihydrochloride salt of Cetirizine.

The novel crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of Cetirizine of the present invention is having significant peaks in X-ray powder diffractogram, which are having the intensity percentages more than 15 are shown in the Table-1. The X-ray powder diffraction pattern is expressed in terms of the 2 theta (degrees), and percentage of intensity (in %).

Table-1:

Dextro rotatory dihydrochloride salt of Cetirizine		**Levo rotatory dihydrochloride salt of Cetirizine**	
2 theta (^{O})	**Intensity (%)**	**2 theta (^{O})**	**Intensity (%)**
18.815	100	18.855	100
25.247	73.2	25.311	79.2
18.170	59.5	18.244	48.9
14.805	35.6	24.211	41.0
24.325	34.6	24.361	40.5
18.591	29.9	8.018	37.2
14.347	29.0	14.87	34.2
24.158	28.2	18.648	30.8
7.955	27.1	23.415	27.5
23.354	27.0	14.408	26.1

17.394	23.4	26.602	24.7
7.053	23.2	22.388	21.6
20.327	21.7	17.475	20.6
22.330	19.5	7.096	19.7
24.727	19.0	24.812	19.5
27.347	17.7	29.282	19.1
30.571	16.8	7.424	18.8
26.514	16.5	20.42	18.7
26.799	16.3	27.385	16.1

The novel crystalline Form-I of Dextro rotatory and levorotatory dihydrochloride salt of Cetirizine of the present invention is having the X-ray powder diffractogram pattern substantially as depicted in Figure (1) and (2) respectively.

The present invention also provides the Differential Scanning Calorimetry thermogram of novel crystalline Form-I of Dextro and levorotatory dihydrochloride salt of Cetirizine. The Differential Scanning Calorimetry thermogram exhibits a similar significant endotherm peaks in between 195 and 215°C.

The present invention further provides the Infrared spectral data for novel crystalline Form-I of dextro and levorotatory dihydrochloride salts of Cetirizine, which were measured by KBr-transmission method with significant peaks at about 3430.22, 2949.03, 2375.88, 1745.88, 1496.74, 1496.74, 1320.06, 1136.79, 919.85, 758.53, 719.86, 700.45 and 534.10 cm^{-1}.

Another embodiment of the present invention is to provide the process for the preparation of novel crystalline Form-I of Dextro and Levorotatory dihydrochloride salts of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Dextro and Levo rotatory dihydrochloride salt of Cetirizine), which comprises;

a. heating the reaction mixture of Levo or Dextro rotatory Cetirizine in ketone solvents comprising of acetone, methyl ethyl ketone, dimethyl

ketone, 2-pentanone or mixture there of, preferably aqueous acetone at a temperature of 40-50^{O}C;

b. optionally subjecting the reaction mixture to carbon treatment;

c. adding aqueous hydrochloric acid or spurging hydrochloric acid gas to the filtrate obtained in step (b) at a temperature of 40-50^{O}C and further stirring for 1-2 hours;

d. cooling the reaction mass obtained in step (c) to an ambient temperature and stirring the mass till the solid separates;

e. filtering the solid obtained in step (d) by conventional methods;

f. optionally subjecting the compound obtained in step (e) for purification in aqueous ketone solvents as described in step (a), preferably aqueous acetone;

g. drying the compound obtained in step (e) or (f) at a temperature of 40-100^{O}C, preferably 55-65^{O}C to afford the desired novel crystalline Form-I of Dextro or Levo rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid.

The crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of cetirizine obtained in the above process are having >99.5% enantiomeric excess purity. The Optical rotation for these crystalline forms have studied in 1% aqueous solution at 365 nm wavelength and found that +12.4° and –12.5° for Dextro and Levorotatory dihydrochloride salts respectively.

The second aspect of the present invention relates to novel amorphous form of Dextro and Levorotatory dihydrochloride salts of Cetirizine and process for preparation thereof.

The novel amorphous form of dihydrochloride salts of Dextro and Levorotatory Cetirizine of the present invention is characterized by X-ray powder diffractogram and both are showing no well-resolved peaks.

The novel amorphous form of Dextro and levorotatory dihydrochloride salts of Cetirizine of the present invention is having the X-ray powder diffractogram pattern substantially as depicted in Figure (3) and (4) respectively.

Yet another embodiment of the present invention is to provide the process for the preparation of novel amorphous form of Dextro and Levorotatory dihydrochloride salts of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Dextro and Levo rotatory dihydrochloride salt of Cetirizine), which comprises;

a. dissolving the Levo or Dextro rotatory dihydrochloride salt of Cetirizine in aqueous ketone solvents comprising of acetone, methyl ethyl ketone, dimethyl ketone, 2-pentanone or mixture there of, preferably aqueous acetone at a temperature of 25-40^{O}C;
b. filtering the reaction solution of step (a) to make the particle free solution;
c. distilling off the solvent from the reaction solution of step (b) under reduced pressure at a temperature of below 80^{O}C till the solid substantially separates;
d. drying the solid obtained in step (c) at a temperature of 40-100^{O}C, preferably 80-90^{O}C to afford the desired novel amorphous form of Dextro or Levo rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid.

The amorphous form of dextro and levo rotatory dihydrochloride salts of Cetirizine obtained in the above process is having moisture content varying from 0.3 to 12.0% by KF method usually the moisture content of these compounds are having around 1.5 to 7.5 % by KF method.

The moisture content of present inventive compounds are measured on Mettler DL-35 instrument using Karl-Fischer reagent.

The present inventive substances are free flowing, non-solvated and thermally stable; hence these may be well suited for pharmaceutical formulations.

The processes of the present invention are simple, eco-friendly and commercially viable.

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

PreparativeExample-1: Preparation of crude Levo rotatory [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Levo rotatory cetirizine):

Dissolved the Levo rotatory 2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethanol (55 grams) in dimethyl formamide (165 ml) and cooled the reaction mixture to a temperature of 0-5^{O}C. Potassium hydroxide (28.0 grams) and sodium mono chloro acetate (29.0 grams) were added to the cooled reaction solution, slowly raised the temperature to room temperature and maintained at the same temperature till the reaction substantially completes. Then the resulting reaction mass was diluted with water (605 ml) and heated to a temperature of 40-50^{O}C, accompanied by washing the reaction mass with toluene (4x110 ml). Then adjusted the P^{H} of the aqueous layer to 4.0-4.5 with concentrated hydrochloric acid, accompanied by extracting the reaction mass with dichloromethane (2x165 ml). Washed the resulting organic layer with 10% sodium

chloride solution (2x165 ml) followed by water (2x165 ml). Carbon (2.7 grams) was added to the washed organic layer and heated to reflux temperature. Then the reaction mass was filtered and washed with dichloromethane (55 ml) followed by evaporating solvent under vacuum to yield the crude Levo rotatory [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid in residual mass (60.6 grams).

PreparativeExample-2: Preparation of crude Dextro rotatory [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Dextro rotatory cetirizine):

Dextro rotatory 2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethanol (105 grams) was added to the stirred reaction mixture of dimethyl formamide (357 ml) and Potassium hydroxide (53.3 grams) accompanied by cooling the reaction mixture to a temperature of 0-5^{O}C. Sodium mono chloro acetate (55.5 grams) was added to the cooled reaction solution, slowly raised the temperature to room temperature and maintained at the same temperature till the reaction substantially completes. Then the resulting reaction mass was diluted with water (1155 ml) and separated the bi-layer mixture accompanied by adjusting the P^{H} of resulting aqueous layer to 9.5 with hydrochloric acid. Then further separated the aqueous layer and washed with ethyl acetate (280x1+245x2 ml) accompanied by separation of aqueous layer form organic layer. Then adjusted the P^{H} of the aqueous layer to 4.0-4.5 with concentrated hydrochloric acid, accompanied by extracting the reaction mass with dichloromethane (385x1+2x245 ml). Washed the resulting total organic layer with 10% sodium chloride solution (1x200 ml) followed by water (200 ml). The solvent from the resulting organic layer was evoporated under

vacuum to yield the crude Dextro rotatory [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid.

(Weight: 123.0 grams).

Example-1:

Preparation of novel crystalline Form-I of Dextro rotatory dihydrochloride salt of Cetirizine:

The crude Levo rotatory [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (56.6 grams, prepared as per the Preparative Example-1) was dissolved in acetone (825 ml) and heated to a temperature of 40-45^{O}C. Hydrochloric acid (32.0 ml) was added and stirred the mass till the solid separates. Then separated solid was filtered, washed with acetone (55 ml) and dried at a temperature of 55-60^{O}C to get the required crude product of Dextro rotatory dihydrochloride salt of 2-[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Dextro rotatory dihydrochloride salt of Cetirizine) (42.0 grams). Thus resulted crude product (40.0 grams) was further purified in aqueous acetone to yield the required novel crystalline Form-I of Dextro rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid.

(Weight: 33.9 grams, Optical Rotation = (+) 12.5^{0}, C=1% in water at 365 nm).

Example-2:

Preparation of novel crystalline Form-I of Levo rotatory dihydrochloride salt of Cetirizine:

Heated the reaction mixture of Dextro rotatory [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid ([110 grams] prepared as per the Preparative

Example-2) and acetone (1100 ml) at a temperature of 40-50^{O}C. Carbon (5.5 grams) was added to the resulting hot reaction mixture and stirred at the same temperature for 15-30 minutes accompanied by filtering and washing with acetone (550 ml). Then hydrochloric acid (64 ml) was added to the resulting filtrate at a temperature of 40-50^{O}C and continued stirring for 1-2 hours. Then cooled the reaction mass to room temperature and stirred for 1-2 hours to separate the solid. The separated solid was filtered, washed with acetone (550 ml) and dried at a temperature of 55-65^{O}C to yield the required novel crystalline Form-I of Levo rotatory dihydrochloride salt of pure [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (71.4 grams). Thus resulted crude product (70.0 grams) was further purified in aqueous acetone to yield the required novel crystalline Form-I of Dextro rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid.

(Weight: 58.5 grams, Optical Rotation: (-) 12.2^{0}, C=1% in water at 365 nm).

Example-3:

Preparation of novel amorphous form of Dextro rotatory dihydrochloride salt of Cetirizine:

Crystalline dextrorotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (10 grams) was dissolved in mixture of acetone (40 ml) and water (100 ml) at 25-40^{O}C. Filtered off the clear solution to eliminate the particles. The solvent was distilled off from the filtered clear solution at below 80^{O}C under vacuum till the solid separates. The separated solid was taken out and further dried at a temperature of 80-90^{O}C to a constant weight to afford the novel amorphous form of title compound.

(Weight: 9.5 grams, M.C. by KF: 1.5%, Optical Rotation = (+) 12.1^{O}, C=1 in water at 365 nm).

Example-4:

Levorotatory Cetirizine (10 grams) was dissolved in a mixture of water (40 ml) and acetone (100 ml) at the room temperature. Hydrochloric acid (10 ml) was added to reaction mixture and stirred for 10 to 30 min at a temperature of 30 to 35 ° C. Then, the reaction solution was filtered and distilled off the solvent completely to dryness at a temperature of below 80 ° C. Cyclohexane (100 ml) was added to the residual mass and stirred for 30-60 minutes at a temperature of 30-35^{O}C. The obtained product was filtered and washed with cyclohexane (50 ml) and on subsequent drying at a temperature of 80-85 ° C to a constant weight resulted the novel amorphous form of dextrorotatory dihydrochloride salt of Cetirizine.

(Weight: 9.9 grams)

Example-5:

Preparation of novel amorphous form of Levo rotatory dihydrochloride salt of Cetirizine:

Crystalline Levorotatory dihydrochloride salt of Cetirizine (5.0 grams) was dissolved in a mixture of acetone (20 ml) and water (50 ml) further the reaction mixture was stirred at a temperature of 25-35^{O}C to get a clear solution. The reaction solution was filtered and solvent was distilled off from the reaction solution completely to dryness at a temperature of 50-75^{O}C under reduced pressure to result the amorphous form of Levo Cetirizine dihydrochloride. The amorphous form of Levo Cetirizine dihydrochloride was further

dried at a temperature of 65-70 °C to a constant weight to afford the novel amorphous form of Levo Cetirizine dihydrochloride.

(Weight: 4.2 grams; M.C. by KF: 5.8%, Optical Rotation = (-) 11.7°, C=1 in water at 365 nm).

Example-6:

Dextro Cetirizine (5 grams) was dissolved in a mixture of water (20 ml) and acetone (50 ml) at the room temperature. Hydrochloric acid (5 ml) was added to reaction mixture and stirred for 10 to 30 min at a temperature of 30 to 35 ° C. Then, the reaction solution was filtered and distilled off the solvent completely to dryness at a temperature of below 80 ° C. Cyclohexane (50 ml) was added to the residual mass and stirred for 30 minutes at a temperature of 30-35°C. The obtained product was filtered and washed with cyclohexane (25 ml) and on subsequent drying at a temperature of 60-110 ° C to a constant weight resulted the novel amorphous form of Levo rotatory dihydrochloride salt of cetirizine

(Weight: 4.7 grams, M.C by KF: 1.7%)

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWINGS

Fig.1 is a characteristic X-ray powder diffraction pattern of novel crystalline Form-I of Dextro rotatory dihydrochloride salt of Cetirizine.

Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees).

The significant 2-theta values are 7.053, 7.955, 14.347, 14.805, 17.394, 18.170, 18.591, 18.815, 20.327, 22.330, 23.354, 24.158, 24.325, 24.727, 25.247, 26.514, 26.799, 27.347 and 30.571two-theta degrees.

Fig.2 is a characteristic X-ray powder diffraction pattern of novel crystalline Form-I of Levo rotatory dihydrochloride salt of Cetirizine.

Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees).

The significant 2-theta values are 7.096, 8.018, 14.408, 14.87, 17.475, 18.244, 18.648, 18.855, 22.388, 23.415, 24.211, 24.361, 24.812, 25.311, 26.602 and 29.282 two-theta degrees.

Fig: 3 is characteristic X-ray powder diffraction pattern of novel amorphous form of Dextro rotatory dihydrochloride salt of Cetirizine.

Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees).

It shows a plain halo with no peaks, which is characteristic of the amorphous nature of product.

Fig: 4 is characteristic X-ray powder diffraction pattern of novel amorphous form of Levo rotatory dihydrochloride salt of Cetirizine.

Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees).

It shows a plain halo with no peaks, which is characteristic of the amorphous nature of product.

We claim:

1. A novel crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Dextro and Levo rotatory dihydrochloride salts of Cetirizine).
2. The novel crystalline Form-I of dihydrochloride salts of Cetirizine as claimed in claim 1 is Dextro rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid (Dextro rotatory dihydrochloride salt of Cetirizine).
3. The novel crystalline Form-I of dihydrochloride salts of Cetirizine as claimed in claim 1 is Levo rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid (Levo rotatory dihydrochloride salt of Cetirizine).
4. The novel crystalline Form-I of Dextro rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid of claim 2 has X-ray Powder diffraction pattern with significant 2-theta values are 7.053, 7.955, 14.347, 14.805, 17.394, 18.170, 18.591, 18.815, 20.327, 22.330, 23.354, 24.158, 24.325, 24.727, 25.247, 26.514, 26.799, 27.347 and 30.571two-theta degrees.
5. The novel crystalline Form-I of Dextro rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid of claims 2 and 4, which provides X-ray powder diffraction pattern substantially in accordance with Figure (1).
6. The novel crystalline Form-I of Levo rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid of claim 3 has X-ray Powder diffraction pattern with significant 2-theta values 7.096, 8.018, 14.408, 14.87,

17.475, 18.244, 18.648, 18.855, 22.388, 23.415, 24.211, 24.361, 24.812, 25.311, 26.602 and 29.282 two-theta degrees.

7. The novel crystalline Form-I of Levo rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid of claims 3 and 6, which provides X-ray powder diffraction pattern substantially in accordance with Figure (2).

8. A process for the preparation of novel crystalline Form-I of Dextro and Levo rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid, which comprises;

   a. heating the reaction mixture of Levo or Dextro rotatory Cetirizine in ketone solvents comprising of acetone, methyl ethyl ketone, dimethyl ketone, 2-pentanone or mixture there of, preferably acetone at a temperature of 40-50^{O}C;
   b. optionally subjecting the reaction mixture to carbon treatment;
   c. adding aqueous hydrochloric acid or spurging hydrochloric acid gas to the filtrate obtained in step (b) at a temperature of 40-50^{O}C and further stirring for 1-2 hours;
   d. cooling the reaction mass obtained in step (c) to an ambient temperature and stirring the mass till the solid separates;
   e. filtering the solid obtained in step (d) by conventional methods;
   f. optionally subjecting the compound obtained in step (e) for purification in aqueous ketone solvents as described in step (a), preferably aqueous acetone;

g. drying the compound obtained in step (e) or (f) at a temperature of 40-100°C, preferably 55-65°C to afford the desired novel crystalline Form-I of Dextro or Levo rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid.

9. The process according to steps (a) and (f) of claim 8, where in the said ketone solvent is acetone.

10. A novel amorphous form of Dextro and Levorotatory dihydrochloride salts of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Dextro and Levo rotatory dihydrochloride salts of Cetirizine).

11. The novel amorphous form of dihydrochloride salts of Cetirizine as claimed in claim 10 is Dextro rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid (Dextro rotatory dihydrochloride salt of Cetirizine).

12. The novel amorphous form of dihydrochloride salts of Cetirizine as claimed in claim 10 is Levo rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid (Levo rotatory dihydrochloride salt of Cetirizine).

13. The amorphous form of dextrorotatory dihydrochloride salt of Cetirizine according to claim 11, which provides X-ray powder diffraction pattern substantially in accordance with Figure (3).

14. The amorphous form of levorotatory dihydrochloride salt of Cetirizine according to claim 12, which provides X-ray powder diffraction pattern substantially in accordance with Figure (4).

15. The amorphous form of dextro and levo rotatory dihydrochloride salt of Cetirizine of claims 11 and 12, which is having moisture content varying from 0.3 to 12.0% by KF method.

16. The amorphous form of dextro and levo rotatory dihydrochloride salt of Cetirizine of claim 15, which is having moisture content from 1.5 to 7.5 % by KF method.

17. A process for the preparation of novel amorphous form of Dextro and Levorotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid, which comprises;

    a) dissolving the Levo or Dextro rotatory dihydrochloride salt of Cetirizine in aqueous ketone solvents comprising of acetone, methyl ethyl ketone, dimethyl ketone, 2-pentanone or mixture there of, preferably aqueous acetone at a temperature of 25-40^{O}C;

    b) filtering the reaction solution of step (a) to make the particle free solution;

    c) distilling off the solvent from the reaction solution of step (b) under reduced pressure at a temperature of below 80^{O}C till the solid substantially separates;

    d) drying the solid obtained in step (c) at a temperature of 40-100^{O}C, preferably 80-90^{O}C to afford the desired novel amorphous form of Dextro or Levo rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid.

18. The process according to step (a) of claim 17, where in the said ketone solvent is acetone.

19. The processes for the preparation of novel crystalline Form-I and amorphous forms of Dextro and Levo rotatory dihydrochloride salt of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid are substantially as here in described and exemplified.

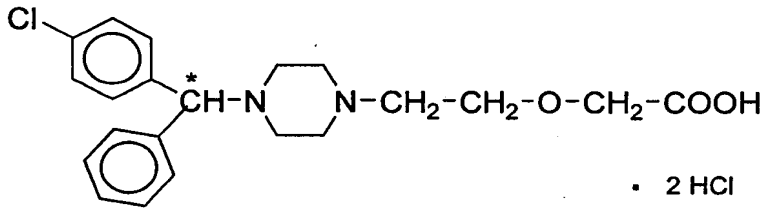
Dated this 29th day of November 2002 Signed)

Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr. Reddy's Laboratories Limited.

ABSTRACT

Title of the Invention: "Novel Polymorphic forms of Dextro and Levo rotatory dihydrochloride salts of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Dextro and Levo rotatory dihydrochloride salts of Cetirizine)"

The present invention relates to novel Polymorphic forms of Dextro and Levorotatory dihydrochloride salts of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid (Dextro and Levo rotatory dihydrochloride salts of Cetirizine), which can be depicted as following Formula (I).



Formula (I)

The first aspect of the present invention relates to the novel crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of Cetirizine and process for preparation there of. The process for the preparation of crystalline Form-I of Dextro and Levo rotatory dihydrochloride salts of Cetirizine comprises the purification of crude dihydrochloride salt of Dextro or Levo rotatory Cetirizine in aqueous keto solvents such as aqueous acetone to afford the novel crystalline Form-I of Dextro or Levo rotatory dihydrochloride salt of Cetirizine.

The second aspect of the present invention relates to the novel amorphous form of Dextro and Levo rotatory dihydrochloride salts of Cetirizine and the process for the preparation there of.

The process for the preparation of novel amorphous form of Dextro and Levo rotatory dihydrochloride salts of Cetirizine comprises the dissolution of crude dihydrochloride salt of Dextro or Levo rotatory Cetirizine in aqueous keto solvents such as aqueous acetone and subjecting the resultant solution to flash distillation under reduced pressure to afford the novel amorphous form of Dextro or Levo rotatory dihydrochloride salts of Cetirizine. The processes of the present invention are simple, eco-friendly and commercially viable.

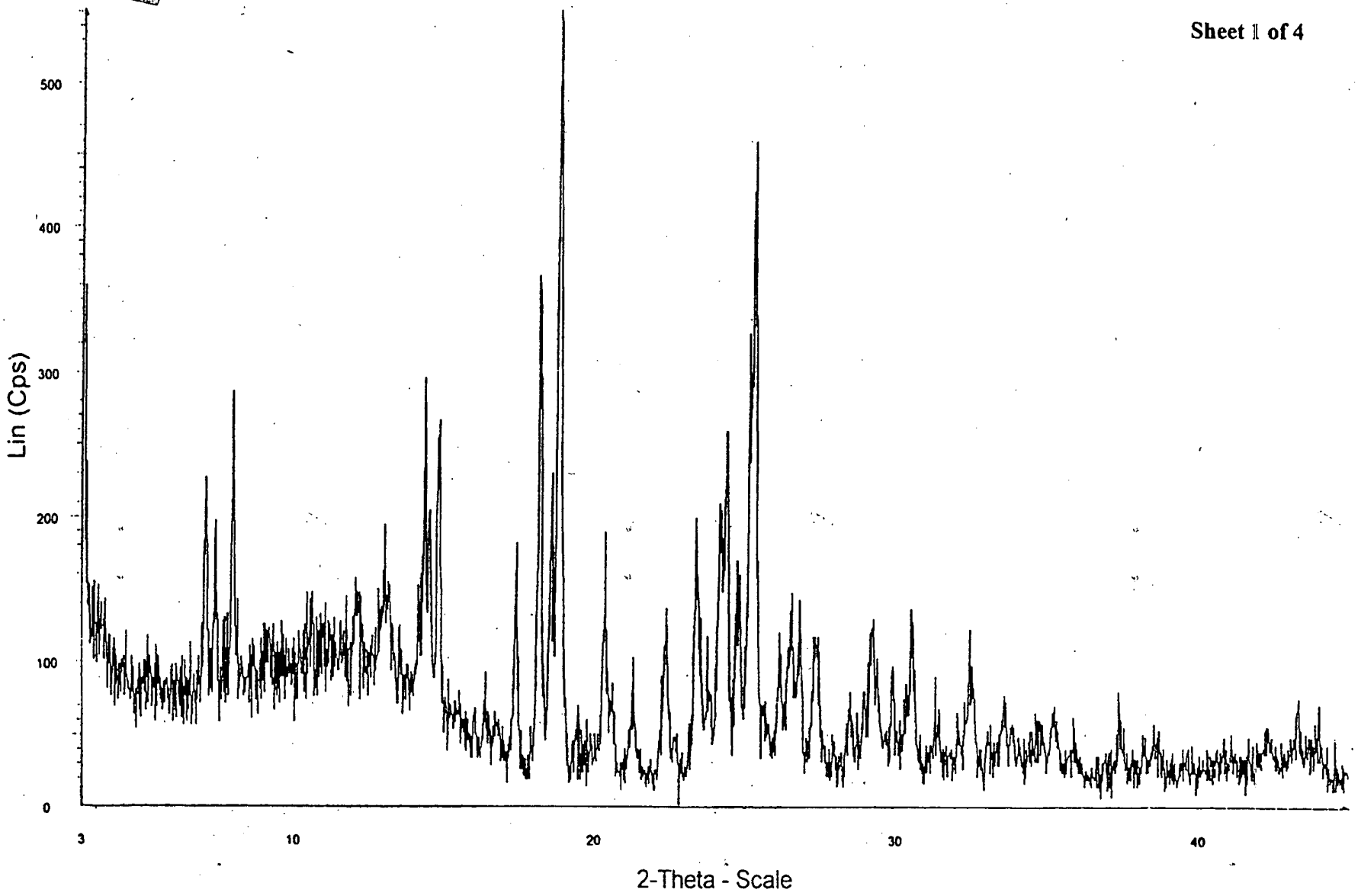


Fig. 1

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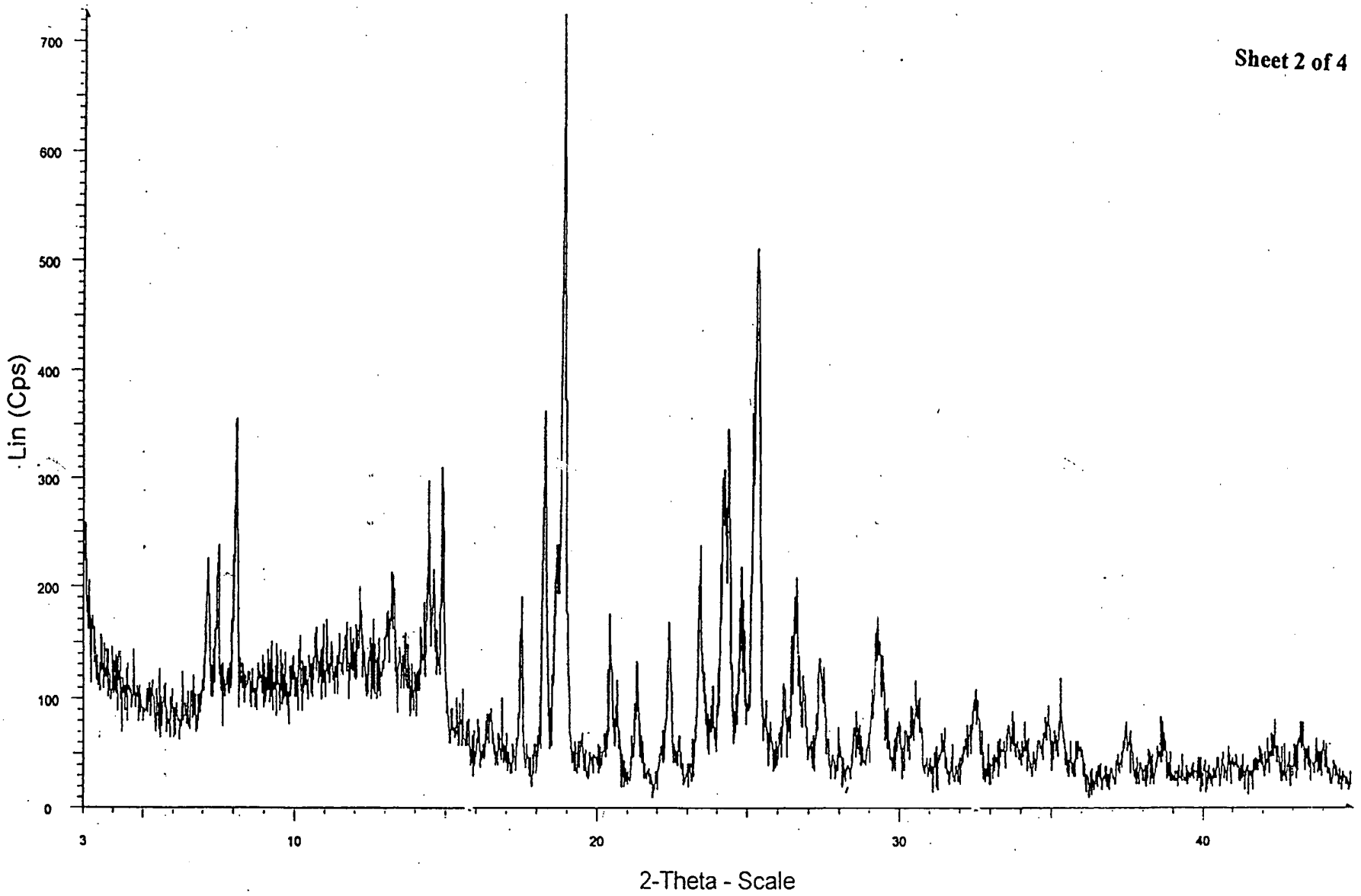

Fig. 2

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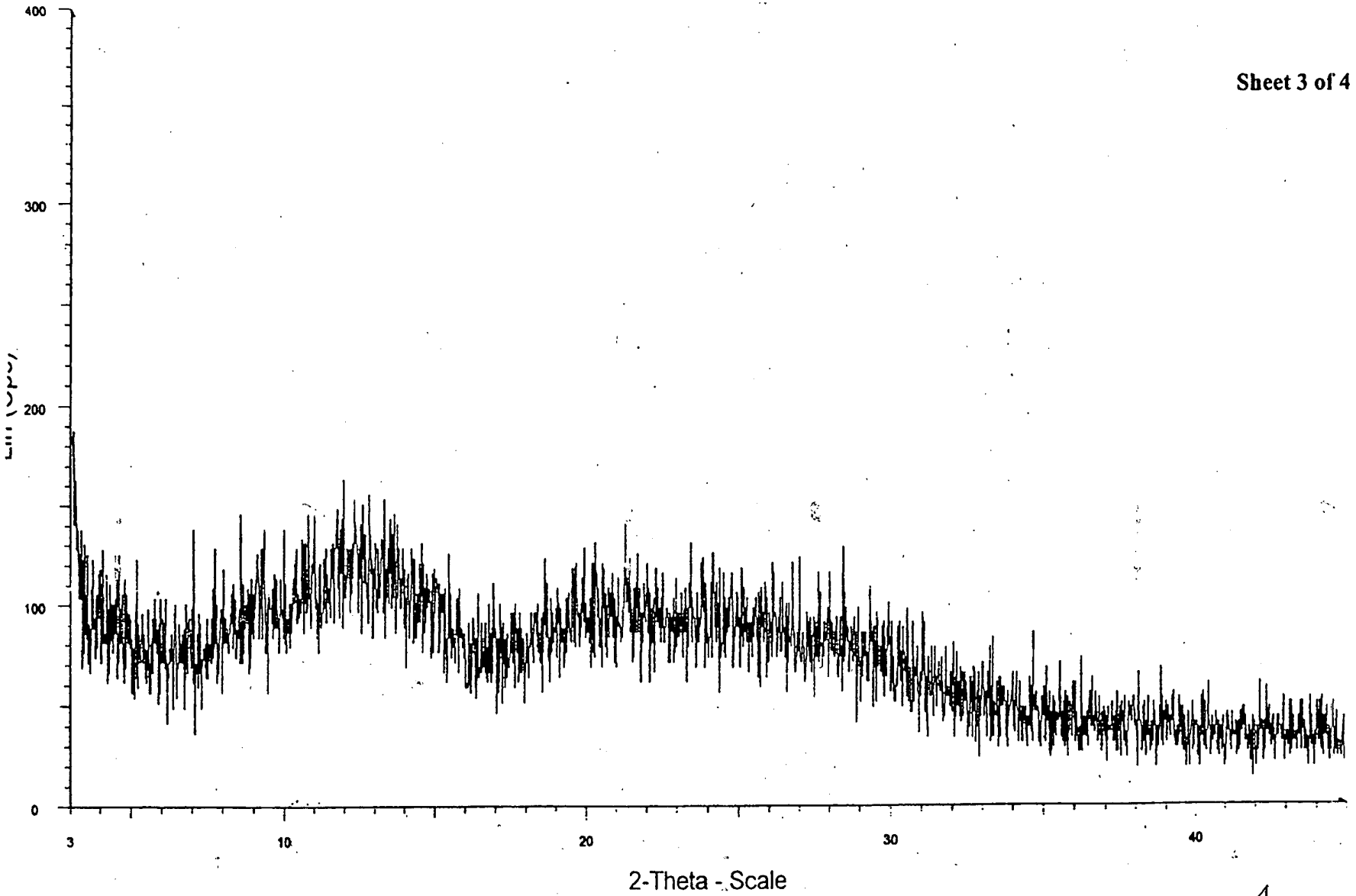

Fig. 3

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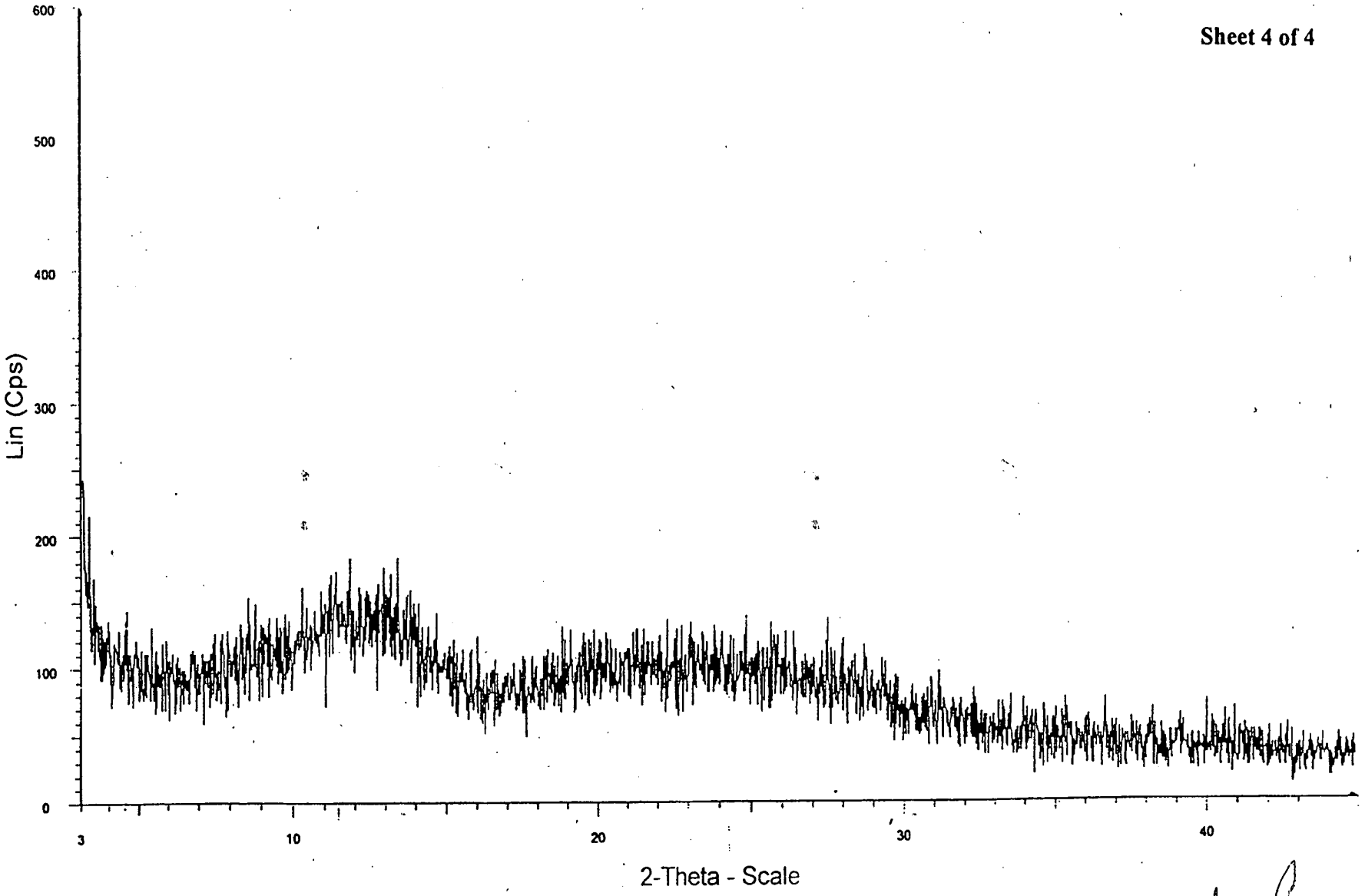

Fig. 4

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